

Heart failure with preserved ejection fraction and atrial fibrillation: vicious twins

Kotecha, Dipak; Lam, Carolyn S.P.; van Veldhuisen, Dirk J; Van Gelder, Isabelle C; Voors, Adriaan A. ; Rienstra, Michiel

DOI:

[10.1016/j.jacc.2016.08.048](https://doi.org/10.1016/j.jacc.2016.08.048)

License:

Creative Commons: Attribution-NonCommercial-NoDerivs (CC BY-NC-ND)

Document Version

Peer reviewed version

Citation for published version (Harvard):

Kotecha, D, Lam, CSP, van Veldhuisen, DJ, Van Gelder, IC, Voors, AA & Rienstra, M 2016, 'Heart failure with preserved ejection fraction and atrial fibrillation: vicious twins', *Journal of the American College of Cardiology*, vol. 68, no. 20, pp. 2217. <https://doi.org/10.1016/j.jacc.2016.08.048>

[Link to publication on Research at Birmingham portal](#)

Publisher Rights Statement:

Eligibility for repository: Checked on 10/4/2017

General rights

Unless a licence is specified above, all rights (including copyright and moral rights) in this document are retained by the authors and/or the copyright holders. The express permission of the copyright holder must be obtained for any use of this material other than for purposes permitted by law.

- Users may freely distribute the URL that is used to identify this publication.
- Users may download and/or print one copy of the publication from the University of Birmingham research portal for the purpose of private study or non-commercial research.
- User may use extracts from the document in line with the concept of 'fair dealing' under the Copyright, Designs and Patents Act 1988 (?)
- Users may not further distribute the material nor use it for the purposes of commercial gain.

Where a licence is displayed above, please note the terms and conditions of the licence govern your use of this document.

When citing, please reference the published version.

Take down policy

While the University of Birmingham exercises care and attention in making items available there are rare occasions when an item has been uploaded in error or has been deemed to be commercially or otherwise sensitive.

If you believe that this is the case for this document, please contact UBIRA@lists.bham.ac.uk providing details and we will remove access to the work immediately and investigate.

Heart Failure With Preserved Ejection Fraction and Atrial Fibrillation: Vicious Twins

Brief title: HF With Preserved Ejection Fraction and AF

<AU>Dipak Kotecha, MD, PhD,^a Carolyn S.P. Lam, MD, PhD,^b Dirk J. Van Veldhuisen, MD, PhD,^c Isabelle C. Van Gelder, MD, PhD,^c Adriaan A. Voors MD, PhD,^c Michiel Rienstra, MD, PhD^c

From the ^aInstitute of Cardiovascular Sciences, University of Birmingham, Birmingham, United Kingdom; ^b Department of Cardiology, National Heart Centre Singapore, Singapore; ^cUniversity of Groningen, University Medical Center Groningen, Groningen, The Netherlands.

Drs. Kotecha and Lam are joint first authors.

Disclosures: No specific funding was used for this review. Dr. Kotecha is supported by a National Institute of Health Research (NIHR) Career Development Fellowship. Dr. Kotecha reports nonfinancial professional development support from Daiichi Sankyo and research grants from Menarini, all outside the submitted work; and Lead for the Beta-blockers in Heart Failure Collaborative Group (BB-meta-HF) and the RAte control Therapy Evaluation in Atrial Fibrillation (RATE-AF) trial. Dr. Lam reports grants from Boston Scientific, Bayer, ThermoFisher, Medtronic, and Vifor Pharma, and personal fees from Bayer, Novartis, Takeda, Merck, Astra Zeneca, Janssen Research & Development, LLC, and Menarini, all outside the submitted work. Dr. Van Veldhuisen reports grant from St.Jude Medical, outside the submitted work, and is a member of steering committees with Novartis and Corvia Medical in the field of HFpEF, for which travel expenses and/or board membership fees have been received. Dr. Van Gelder reports grants from Medtronic and the Dutch Heart Foundation, outside the submitted work. Dr. Voors reports having received research support from Novartis and consultancy fees from Boehringer Ingelheim, Novartis, and Servier. Drs. Van Gelder and Rienstra acknowledge support from the Netherlands Cardiovascular Research Initiative; an initiative with support of the Dutch Heart Foundation (CVON 2014-9: Reappraisal of Atrial Fibrillation - interaction between hypercoagulability, electrical remodeling, and vascular destabilisation in the progression of AF [RACE V]). Dr. Rienstra has no relationships relevant to the contents of this paper to disclose. The opinions expressed in this paper are those of the authors, and do not represent the NIHR or the U.K. Department of Health.

<COR>Reprint requests and correspondence:

Dr. Michiel Rienstra, MD, PhD

Department of Cardiology

University of Groningen, University Medical Center Groningen

P.O. Box 30.001

9700 RB Groningen

The Netherlands

Telephone +31 50 3612355

Fax +31 50 3614391

E-mail: m.rienstra@umcg.nl

Abstract

Heart failure with preserved ejection fraction (HFpEF) and atrial fibrillation (AF) are age-related conditions that are increasing in prevalence, commonly coexist, and share clinical features. This review provides a practical update on the epidemiology, pathophysiology, diagnosis, and management of patients with concomitant HFpEF and AF. Epidemiological studies highlight the close and complex links between HFpEF and AF, the shared risk factors, the high AF occurrence in the natural history of HFpEF, and the independent contribution of each condition to poor outcomes. Diagnosis of HFpEF in the setting of AF is challenging because the symptoms overlap. AF is associated with changes in echocardiographic parameters and circulating natriuretic peptides that confound HFpEF diagnosis. Symptomatic improvement with diuretic therapy supports the presence of HFpEF in patients with concomitant AF. Important knowledge gaps need to be addressed by a multidisciplinary and translational research approach, in order to develop novel therapies that can improve prognosis.

<KW>Key words: Age; Diagnosis; Epidemiology; Natriuretic Peptides, Outcomes

Abbreviations and Acronyms

AF = atrial fibrillation

ANP = atrial natriuretic peptide

HF = heart failure

HFpEF = heart failure with preserved ejection fraction

HFrfEF = heart failure with reduced ejection fraction

LA = left atrium/atrial

LV = left ventricular

LVEF = left ventricular ejection fraction

NT-proBNP = N-terminal B-type natriuretic peptide

Introduction

Heart failure with preserved ejection fraction (HFpEF) and atrial fibrillation (AF) are common conditions that are increasing in prevalence, and are associated with increased morbidity and mortality compared with patients without these diagnoses (1). HFpEF is as common as heart failure with reduced ejection fraction (HFrEF), and patients suffer from similar symptoms, yet lack therapeutic options with proven efficacy (2). Patients with AF are heterogeneous and share many common clinical features with patients with heart failure (HF), but demonstrate a requirement for specific management in order to improve outcomes, over and above related comorbidities (3). Both HFpEF and AF are associated with older age, hypertension, and diastolic dysfunction; therefore, these disorders are inextricably linked, both to each other and to adverse cardiovascular outcomes (1). AF is a potent and independent prognostic factor in patients with HF, increasing the risk of death in clinical trials and observational studies (4,5). The development of AF may have more of an impact in patients with HFpEF than in those with HFrEF (6,7), identifying a subgroup of patients with more advanced HFpEF and worse exercise tolerance (8). Although the combination of AF and HFpEF appears to be associated with lower mortality than AF and HFrEF, patients have similar rates of incident stroke and HF hospitalization (9). Furthermore, the severity of disease in HFpEF and HFrEF may not have been comparable in prior studies. At the very least, AF and HF require comparable attention.

Not all studies have been able to differentiate whether HFpEF or AF comes first, and there are clear diagnostic challenges in clinical practice. Identifying prevalent AF in the context of HFpEF is relatively straightforward, with well-documented electrocardiographic methods that apply to a wide range of patient populations (10). However, AF is often paroxysmal, frequently

asymptomatic, and can be easily missed (11). HFpEF remains a clinical diagnosis (12,13), combining typical symptoms and signs with echocardiographic evidence of diastolic dysfunction and “preserved” left ventricular ejection fraction (LVEF). Importantly, symptoms like dyspnea, fatigue, and impaired exercise tolerance are also the predominant symptoms of patients with AF, and largely overlap with HFpEF, making definitive diagnosis on the basis of clinical features more complex. There is ambiguity in echocardiographic diagnosis, both for the LVEF cutoff (which is a continuum), and the objective evaluation of diastolic function, which is not always easy or possible to demonstrate, particularly in the context of AF. Circulating levels of biomarkers, such as N-terminal B-type natriuretic peptides (NT-proBNPs) are also independently influenced by both conditions, making it unclear what NT-proBNP levels to use for the diagnosis of one condition in the presence of the other (2).

In this review, we aim to focus on the epidemiology, pathophysiology, diagnosis, and management of patients with concomitant HFpEF and AF. We start by summarizing available evidence regarding the prevalence and incidence of HFpEF in the setting of AF and vice versa, and then examine the underlying mechanisms by which AF begets HFpEF and HFpEF begets AF. Further, we address the diagnostic uncertainties of each condition in the presence of the other, and consider potential therapeutic strategies. Our objective is to provide clinicians with a practical guide to the key issues, and address the knowledge gaps that prevent optimal treatment of this common and high-risk group of patients.

Incidence and prevalence of HFpEF in the setting of AF

Data on the incidence and prevalence of clinical HF in patients with AF is widely available, however specific studies on HFpEF are scarce. The PREVEND (Prevention of Renal and Vascular End-Stage Disease) study is a community-based cohort in the Netherlands. Of

8,265 participants studied, 265 developed AF (total follow-up 80,352 person-years). The incidence rate of HFpEF (LVEF >50%) per 1,000 person-years was 4.90 for those with AF versus 0.85 for those without AF, a hazard ratio (HR) of 4.8 (1). AF was identified as a major risk factor for new-onset HFpEF in the Framingham Heart Study (HR: 2.5), and the presence of AF tended to predict incident HFpEF (HR: 2.3) more strongly than in HFrEF (14). Furthermore, among participants with AF, there was a higher incidence of HFpEF in women compared to men (35.1 vs. 21.2 events/1,000 person-years) (15). Surveys, registries, and trials give further insight the prevalence of HFpEF is in patients with AF, which varies between 8% and 24% (16-19), and depends on the definition (LVEF above 40% or 50%), and the type of AF (**Figure 1**). Although different definitions of HFpEF were used, it would seem prudent to suggest that HFpEF is more common in those with a longer duration of AF.

Incidence and prevalence of AF in the setting of HFpEF

Large epidemiological studies have established that HF is a potent risk factor for incident AF, with a 6-fold increase in the risk of developing AF in a previous report from the Framingham Heart Study (20). In fact, AF is the most common arrhythmia in HF, present in around one-third of patients (21,22). The prevalence of AF increases with HF severity, ranging from 5% in mild HF to 50% in severe HF (23). Specifically for HFpEF, the prevalence of AF varies between 15% and 41% (**Figure 2**).

The temporal progression of AF in HFpEF was described in 939 participants with newly diagnosed HFpEF in the Olmsted County population cohort. Two-thirds experienced AF during the course of their disease: 29% prior to diagnosis, 23% concurrent with HFpEF, and 15% after diagnosis (24). Participants with prevalent AF at the time of HFpEF diagnosis (compared to sinus rhythm) were older and had higher NT-proBNP levels and larger left atria, whereas those

with incident AF after HFpEF diagnosis had greater diastolic dysfunction. More recently, a study of the temporal associations of AF and HFpEF versus HFrEF showed that participants with HFpEF were more likely to have prevalent AF compared to HFrEF (32% vs. 23%, $p = 0.002$) and AF at any time (62% vs. 55%, $p = 0.02$) (15). In aggregate, these studies highlight the close and complex links between HFpEF and AF, the extraordinarily high occurrence of AF in the natural history of HFpEF, and the independent contribution of each condition to poor outcomes in affected patients.

Shared pathophysiology

Given that a substantial proportion of patients with HFpEF experience AF at some point during the course of their disease, shared pathophysiological mechanisms are highly likely. These may involve: 1) common risk factors and comorbidities that predispose to both conditions simultaneously; 2) mechanisms by which HFpEF gives rise to AF; and 3) mechanisms by which AF leads to HFpEF (**Figure 3**). Noncardiac comorbidities are often present in HFpEF. Pulmonary disease, diabetes mellitus, anemia, and obesity tend to be more prevalent in HFpEF patients, but renal disease and sleep-disordered breathing burdens are similar to HFrEF (25). These comorbidities are also frequently present in the setting of AF (26).

Common risk factors predisposing to both HFpEF and AF simultaneously

Common risk factors prominently shared between HFpEF and AF include advanced age and age-related comorbidities, such as hypertension, obesity, and sleep apnea. Vascular-ventricular stiffening, the hallmark of aging (27), plays an important role in the pathophysiology of HFpEF via left ventricular (LV) diastolic dysfunction and systolic ventricular-vascular uncoupling (28,29). Similarly, the incidence of AF increases sharply with age (30), and age-related diastolic dysfunction has been shown to contribute to AF in the general population

(31,32). Importantly, however, the incidence of AF in HFpEF exceeds that expected by aging alone (incidence rate of 69 cases/1,000 person-years in Olmsted County HFpEF (24) compared with 28.3/1,000 person-years in U.S. Medicare beneficiaries ≥ 65 years of age) (30).

Systemic inflammation may also link HFpEF and AF, with a new paradigm proposing HFpEF as an inflammatory disorder in which comorbidities, such as obesity, trigger widespread endothelial dysfunction, oxidative stress, and microvascular inflammation, leading to end-organ manifestations, such as diastolic dysfunction (33,34). Evidence supporting the hypothesis of endothelial microvascular inflammation in HFpEF accumulates, although definitive clinical trial data are still lacking. Histological findings in atrial biopsies support the proinflammatory milieu of HFpEF as a key mechanism underlying AF occurrence and maintenance (35). In patients undergoing AF ablation, levels of inflammatory markers, such as C-reactive protein, interleukin-6, and matrix metalloprotease-2, differed significantly between those who remained in sinus rhythm after ablation versus patients who reverted to AF (36).

Mechanisms by which HFpEF gives rise to AF

The most commonly recognized mechanism by which HFpEF gives rise to AF is via structural and functional remodeling of the left atrium (LA). LA volumes are 68% larger in HFpEF compared with age-matched controls, and 40% larger than in patients with hypertensive heart disease without HF (37). Patients with HFpEF have reduced emptying fractions and contractile reserve, compared with controls and patients with hypertension. LA enlargement in HFpEF is a well-established proarrhythmic substrate associated with atrial fibrosis (38). Abnormal distribution of gap junctions and loss of cell-to-cell coupling in areas of fibrosis contributes to electrical remodeling, increased atrial refractoriness, and development of AF (39,40). Disrupted ion-channel regulation has been demonstrated in experimental models of HF,

with reduction in the L-type calcium ion (Ca^{2+}) current, the sensitive transient outward potassium ion (K^+) current and the slow delayed rectifier K^+ current in atrial myocytes (41), whereas the transient inward sodium ion (Na^+)/ Ca^{2+} exchanger current is increased (42). The increase in the Na^+ / Ca^{2+} transmembrane exchange channel current gives rise to delayed afterdepolarizations, leading to arrhythmias initiated by triggered activity (43). The important role of gap junctions in atrial remodeling has also been highlighted, involving atrial connexin proteins (44) and the resultant inhomogeneity of impulse propagation, thus establishing re-entry circuits predisposing to AF. Although many of these seminal AF studies were performed in HFrEF models, the underlying concepts also apply to atrial remodeling in the setting of HFpEF.

Up-regulation of the adrenergic and renin-angiotensin-aldosterone systems have been shown in experimental models to contribute to impaired impulse propagation, atrial fibrosis, and AF in HF. Because both neuroendocrine systems are similarly up-regulated in HFpEF and in HFrEF (45), these mechanisms may underlie the development of AF in HFpEF. A further consideration includes the role of atrial natriuretic peptide (ANP), the hormone produced by the atria in response to stretch, which causes diuresis and vasodilation. Impaired natriuresis has been shown to contribute to volume overload among patients with preclinical diastolic dysfunction (46). Although normally important for homeostasis, failure of the atrium to secrete adequate amounts of ANP in HFpEF may be associated with atrial structural remodeling and mechanical dysfunction (47). Interestingly, atrial endocrine failure may be addressed by blocking neprilysin, the neutral endopeptidase that breaks down ANP.

Mechanisms by which AF gives rise to HFpEF

Because AF itself causes LA dilation, impaired atrial function, and atrial fibrosis, AF may be a direct cause of HFpEF (48). Indeed, successful cardioversion is associated with

restoration of atrial booster pump function and improved ventricular filling, with the atrial contribution to ventricular filling increasing from 30% to 47% one month after the return of sinus rhythm (49). AF is also associated with LV myocardial fibrosis (50), which, in turn, contributes to diastolic dysfunction and HFpEF (51). Furthermore, atrioventricular annular remodeling with progressive mitral and tricuspid regurgitation may be another mechanism by which AF causes HFpEF (52). Also, depletion of ANP, which may occur in permanent AF, may lead to more vasoconstriction and congestion, and set the stage for incident HFpEF (53).

A mechanism often proposed to explain the development of HF in AF is that of tachycardia or irregularity-induced cardiomyopathy, including hemodynamic changes (shortened diastasis, reduced cardiac output), structural effects (LV eccentric remodeling, subendocardial fibrosis, impaired myocardial perfusion), cellular impact (cytoskeletal alteration, matrix and mitochondrial disruption, abnormal calcium handling), and neurohormonal activation (up-regulation of the renin-angiotensin-aldosterone and natriuretic peptides) (54,55). However, these mechanisms classically pertain to HFrEF, and their contribution to HFpEF remains poorly understood. It is also possible that some cases of so-called HFpEF with AF may be patients in whom LVEF has recovered with adequate heart rate control.

Diagnostic uncertainty

Diagnosing HFpEF in the context of AF is challenging. HF remains a clinical syndrome characterized by the concordance of: 1) clinical symptoms and signs; 2) objective evidence of LV diastolic dysfunction; 3) increased circulating natriuretic peptide levels; and 4) response to therapy (12,56). The first 3 diagnostic components are difficult to establish in the presence of AF because symptoms of HF resemble those of AF, echocardiographic parameters of diastolic dysfunction are more challenging to obtain, and natriuretic peptide levels are elevated in patients

with AF, even in the absence of HF. Although reduced LVEF in AF patients can be diagnosed with different cardiac imaging modalities, identifying HFpEF requires a combination of heterogeneous echocardiographic parameters (57). As a result, there is often clinical reluctance to categorically state the presence of HFpEF in coexisting AF. Furthermore, there is considerable variation in the definition of HFpEF regarding the cutoff of LVEF (2). Although current guidelines recommend LVEF $\geq 50\%$, such definitions are arbitrary and may not apply to individual patients. The last of the 4 diagnostic components, response to therapy, seems of potential value, yet is underutilized in HFpEF and AF. Diuretic therapy may provide symptomatic benefit in patients with AF, concomitant HFpEF, and signs of fluid overload (58). Although there are no controlled trials available, improved fluid balance and symptom relief with diuretic therapy, in the absence of any change in heart rate or rhythm, are powerful clinical indicators of the presence of HFpEF in AF patients (**Central Illustration**).

Echocardiography and natriuretic peptides

A number of studies have demonstrated elevated filling pressures in AF, and have validated echocardiographic parameters in AF patients against invasive pulmonary capillary wedge pressure and clinical outcomes. For example, E/e' was significantly associated with filling pressure (5 studies with n = 444; correlation 0.47 to 0.79) (59-63), and independently associated with mortality (64), exercise capacity (65), prior ischemic stroke (66), and quality of life (67). A number of other diastolic indexes also correlate with invasive filling pressure, such as isovolumic relaxation time (IVRT), mitral deceleration time, diastolic flow progression (E/Vp), and pulmonary venous flow measures (68). These results confirm that HFpEF (i.e., the presence of elevated LV filling pressure and HF symptoms) does exist in patients with AF and can be diagnosed, albeit from small observational studies with highly selective inclusion.

The difficulty in making definitive diagnoses of diastolic dysfunction by echocardiography or the presence of HF by elevated levels of natriuretic peptides lies in AF being a known modifier of the relationship between each of these variables and HFpEF. For example, in the case of HFpEF and DproBNP, AF is related to HFpEF and also independently leads to elevation of NT-proBNP, thus potentially distorting the relationship between HFpEF and NT-proBNP. As a result, it remains unclear which NT-proBNP cutoff to use for the diagnosis of HFpEF in the setting of AF, and to what extent NT-proBNP levels respond to treatment (2). Similarly, dilation and dysfunction of the LA, which, in sinus rhythm, is a useful diagnostic criterion for HFpEF (69), may be pre-existing in patients with AF. In most clinical cases, the diagnosis of diastolic dysfunction requires categorizing patients using a range of different parameters (70), not all of which will be abnormal, thus creating clinical uncertainty. These are also critical challenges in designing clinical trials for HFpEF and AF.

Prognosis of concomitant AF and HFpEF

Both prevalent and incident AF are associated with increased mortality in HFpEF (HRs: 1.30 and 2.45, respectively, compared with patients with no AF) (24). Conversely, the presence of HF substantially worsens the prognosis in patients with AF (71,72). However, the type of HF may have different effects on different outcomes. In a meta-analysis of 10 studies, all-cause mortality was significantly higher in patients with HFrEF and AF than in those with HFpEF and AF (risk ratio 1.24, 95% CI: 1.12 to 1.36; $p < 0.001$; $n = 45,100$), whereas HF hospitalization and incident stroke were similar, regardless of ejection fraction (9). In the I-PRESERVE (Irbesartan in Heart Failure With Preserved Ejection Fraction) trial, stroke rates in HFpEF patients were doubled in those with a history of AF, regardless of whether they were in AF at the time of assessment (73). Sex differences in HFpEF were also noted in I-PRESERVE, with a greater

adverse prognostic effect of AF in women compared with men (74). In observational studies, patients in sinus rhythm with HFrEF had markedly worse symptoms, functional capacity, and quality of life compared to patients with HFpEF, whereas in AF patients, there were no differences between HFrEF and HFpEF (75).

Current and future treatment opportunities

There are no treatments for patients with HFpEF and AF that have been shown to improve prognosis, aside from anticoagulation (26,76). HF therapies that reduce mortality and morbidity in HFrEF, such as angiotensin-converting-enzyme inhibitors, angiotensin-receptor blockers, and mineralocorticoid-receptor antagonists, do not have the same impact in HFpEF (77-79). The added consequences of AF may also neutralize the mortality benefit of other therapies, such as beta-blockers or digoxin (5,80).

Anticoagulation in AF patients is required when patients have clinical risk factors for stroke or thromboembolism, and current guidelines highlight the risk associated with both HFrEF and HFpEF on the basis of growing evidence that stroke rates are increased in AF patients with either type of HF (9,81,82). Although no trial has specifically randomized AF patients with HFpEF to anticoagulation, subgroup data from the nonvitamin K antagonist oral anticoagulant (NOAC) trials suggest similar efficacy in patients with and without HF (83).

Other treatments of concomitant HFpEF and AF aim to reduce symptoms and improve quality of life (**Central Illustration**). The mainstay of management is therefore to optimize fluid balance, control blood pressure, and avoid ischemia, in addition to managing comorbidities, such as obesity, airway diseases, and diabetes (3). Aggressive risk factor management programs, including weight loss, have reduced AF recurrences and symptoms in AF patients (84-87) and improved cardiorespiratory fitness in HFpEF patients (88). This supports the notion that

adequate treatment of comorbidities and risk factors may improve symptom burden, quality of life, and improve exercise capacity. Rate control of AF in the context of HFpEF is not expected to improve hard endpoints, and any benefit with regard to quality of life, exercise capacity, or cardiac function are yet to be determined, including in older patients, who form the majority of this group (89). Some data suggest reduced symptoms with rate control, although the AF populations assessed were not specifically those with HF or HFpEF (90,91). In elderly patients with severe symptoms related to HFpEF and AF, it seems reasonable to start with rate control to optimize ventricular filling time and prevent symptoms related to paroxysms of rapid AF. Adopting a rhythm control strategy is challenging in patients with HFpEF; often patients are of advancing age and have multiple other comorbidities that may influence the success and risk of complications. Nevertheless, from a small single-center study, catheter ablation in HFpEF was associated with improved diastolic function in patients who maintained sinus rhythm (albeit with multiple procedures and/or antiarrhythmic drugs) (92). Early rhythm control strategies, which are currently under investigation, may increase the beneficial effects on symptom burden, and potentially improve prognosis (93). More advanced AF ablation techniques, including hybrid epicardial and endocardial ablation, offer promise for reducing the AF burden, even in patients with advanced atrial remodeling, such as those with HFpEF.

Emerging medical therapies offer a glimmer of hope (94). In view of potential atrial endocrine failure in HFpEF with AF (discussed earlier) and the utility of neprilysin inhibitors to restore ANP levels, it is noteworthy that the angiotensin receptor-neprilysin inhibitor LCZ696 reduced LA volume in HFpEF in the PARAMOUNT (Prospective comparison of ARNI with ARB on Management Of heart failUre with preserved ejection fracTion) phase II trial (95). LCZ696 was equally effective in improving outcomes in the presence or absence of AF in the

PARADIGM-HF trial (Prospective comparison of ARNI with ACEi to Determine Impact on Global Mortality and morbidity in Heart Failure) in patients with HFrEF (96).

Implantable cardiac devices may also affect the prognosis in patients with HFpEF, with and without AF. Sudden cardiac death accounts for a sizeable proportion of deaths in HFpEF trials (97,98); however, uncertainty remains regarding the true incidence of sustained ventricular tachyarrhythmia and arrhythmic death in the general HFpEF population. Clarifying this uncertainty is of great importance because this may set the stage for implantable defibrillator therapies in HFpEF. The VIP-HF (Ventricular tachyarrhythmia detection by Implantable Loop Recording in Patients with Heart Failure and Preserved Ejection Fraction) registry is currently recruiting patients, and is due to report in late 2018 (99). Whether cardiac resynchronization therapy (CRT) is beneficial in HFpEF with and without AF needs to be determined. Substudies of CRT trials have shown that patients with less severe LV dysfunction (LVEF >35%) appeared to derive clinical and structural benefit from resynchronization (100). However, as mechanical dyssynchrony in HFpEF differs from that seen in classical HFrEF indications (101), the value of CRT in HFpEF patients with AF needs to be explored in future trials.

Knowledge gaps

Despite the increasing understanding of HFpEF and AF separately, there are still important knowledge gaps. Further study is essential to advance our understanding of the pathogenesis, risk, prevention, and treatment of concomitant HFpEF and AF. In **Table 1** we summarize knowledge gaps and potential future research topics, such as defining the global burden of AF in HFpEF and vice versa, identifying genomic and nongenomic risk factors, determining the clinical effect of rate versus rhythm control, and clarifying optimal heart rate targets. To address these questions, we advocate multidisciplinary and translational research

programs capitalizing on experimental studies, observational community-based cohorts, and clinical trials. There are also opportunities for future research in the area of diagnosis, particularly new cardiac imaging techniques, novel clinical indexes, and measures of LA function.

Summary and conclusions

Although HFpEF and AF frequently coexist, there are still numerous unanswered questions about the pathophysiology, symptomatology, diagnosis, and prognosis of both conditions when occurring together. More systematic research is urgently needed to answer these unresolved issues, and to provide treatments that can improve quality of life and reduce adverse clinical outcomes in the rapidly expanding number of patients with HFpEF and AF.

References

1. Vermond RA, Geelhoed B, Verweij N, et al. Incidence of atrial fibrillation and relationship with cardiovascular events, heart failure, and mortality: a community-based study from the Netherlands. *J Am Coll Cardiol* 2015;66:1000-7.
2. Kelly JP, Mentz RJ, Mebazaa A, et al. Patient selection in heart failure with preserved ejection fraction clinical trials. *J Am Coll Cardiol* 2015;65:1668-82.
3. Kotecha D, Piccini JP. Atrial fibrillation in heart failure: what should we do? *Eur Heart J* 2015;36:3250-7.
4. Mamas MA, Caldwell JC, Chacko S, et al. A meta-analysis of the prognostic significance of atrial fibrillation in chronic heart failure. *Eur J Heart Fail* 2009;11:676-83.
5. Kotecha D, Holmes J, Krum H, et al.; Beta-Blockers in Heart Failure Collaborative Group. Efficacy of β blockers in patients with heart failure plus atrial fibrillation: an individual-patient data meta-analysis. *Lancet* 2014;384:2235-43.
6. Linssen GC, Rienstra M, Jaarsma T, et al. Clinical and prognostic effects of atrial fibrillation in heart failure patients with reduced and preserved left ventricular ejection fraction. *Eur J Heart Fail* 2011;13:1111-20.
7. Olsson LG, Swedberg K, Ducharme A, et al.; CHARM Investigators. Atrial fibrillation and risk of clinical events in chronic heart failure with and without left ventricular systolic dysfunction: results from the Candesartan in Heart failure- Assessment of Reduction in Mortality and morbidity (CHARM) program. *J Am Coll Cardiol* 2006;47:1997-2004.
8. Zakeri R, Borlaug BA, McNulty SE, et al. Impact of atrial fibrillation on exercise

- capacity in heart failure with preserved ejection fraction: a RELAX trial ancillary study. *Circ Heart Fail* 2014;7:123-30.
9. Kotecha D, Chudasama R, Lane DA, et al. Atrial fibrillation and heart failure due to reduced versus preserved ejection fraction: a systematic review and meta-analysis of death and adverse outcomes. *Int J Cardiol* 2016;203:660-6.
 10. Kirchhof P, Breithardt G, Bax J, et al. A roadmap to improve the quality of atrial fibrillation management: proceedings from the fifth Atrial Fibrillation Network/European Heart Rhythm Association consensus conference. *Europace* 2016;18:37-50.
 11. Fetsch T, Bauer P, Engberding R, et al. Prevention of atrial fibrillation after cardioversion: results of the PAFAC trial. *Eur Heart J* 2004;25:1385-94.
 12. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2013;62:e147-239.
 13. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J* 2016;37:2129-200.
 14. Ho JE, Lyass A, Lee DS, et al. Predictors of new-onset heart failure: differences in preserved versus reduced ejection fraction. *Circ Heart Fail* 2013;6:279-86.
 15. Santhanakrishnan R, Wang N, Larson MG, et al. Atrial fibrillation begets heart failure and vice versa: temporal associations and differences in preserved versus reduced ejection fraction. *Circulation* 2016;133:484-92.
 16. Silva-Cardoso J, Zharinov OJ, Ponikowski P, et al.; RealiseAF Investigators. Heart

- failure in patients with atrial fibrillation is associated with a high symptom and hospitalization burden: the RealiseAF survey. *Clin Cardiol* 2013;36:766-74.
17. Lip GY, Laroche C, Popescu MI, et al. Heart failure in patients with atrial fibrillation in Europe: a report from the EURObservational Research Programme Pilot survey on Atrial Fibrillation. *Eur J Heart Fail* 2015;17:570-82.
 18. Badheka AO, Rathod A, Kizilbash MA, et al. Comparison of mortality and morbidity in patients with atrial fibrillation and heart failure with preserved versus decreased left ventricular ejection fraction. *Am J Cardiol* 2011;108:1283-8.
 19. Mulder BA, Van Veldhuisen DJ, Crijns HJ, et al.; RACE II investigators. Lenient vs. strict rate control in patients with atrial fibrillation and heart failure: a post-hoc analysis of the RACE II study. *Eur J Heart Fail* 2013;15:1311-8.
 20. Benjamin EJ, Levy D, Vaziri SM, et al. Independent risk factors for atrial fibrillation in a population-based cohort. The Framingham Heart Study. *JAMA* 1994;271:840-4.
 21. Fonarow GC, Stough WG, Abraham WT, et al.; OPTIMIZE-HF Investigators and Hospitals. Characteristics, treatments, and outcomes of patients with preserved systolic function hospitalized for heart failure: a report from the OPTIMIZE-HF Registry. *J Am Coll Cardiol* 2007;50:768-77.
 22. Maggioni AP, Dahlström U, Filippatos G, et al.; Heart Failure Association of the ESC (HFA). EURObservational Research Programme: the Heart Failure Pilot Survey (ESC-HF Pilot). *Eur J Heart Fail* 2010;12:1076-84.
 23. Maisel WH, Stevenson LW. Atrial fibrillation in heart failure: epidemiology, pathophysiology, and rationale for therapy. *Am J Cardiol* 2003;91:2D-8D.
 24. Zakeri R, Chamberlain AM, Roger VL, et al. Temporal relationship and prognostic

- significance of atrial fibrillation in heart failure patients with preserved ejection fraction: a community-based study. *Circulation* 2013;128:1085-93.
25. Mentz RJ, Kelly JP, von Lueder TG, et al. Noncardiac comorbidities in heart failure with reduced versus preserved ejection fraction. *J Am Coll Cardiol* 2014;64:2281-93.
 26. Kirchhof P, Benussi S, Kotecha D, et al. 2016 ESC guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J* 2016 Aug 27 [E-pub ahead of print], <http://dx.doi.org/10.1093/eurheartj/ehw210>.
 27. Redfield MM, Jacobsen SJ, Borlaug BA, et al. Age- and gender-related ventricular-vascular stiffening: a community-based study. *Circulation* 2005;112:2254-62.
 28. Lam CS, Roger VL, Rodeheffer RJ, et al. Cardiac structure and ventricular-vascular function in persons with heart failure and preserved ejection fraction from Olmsted County, Minnesota. *Circulation* 2007;115:1982-90.
 29. Kawaguchi M, Hay I, Fetics B, et al. Combined ventricular systolic and arterial stiffening in patients with heart failure and preserved ejection fraction: implications for systolic and diastolic reserve limitations. *Circulation* 2003;107:714-20.
 30. Piccini JP, Hammill BG, Sinner MF, et al. Incidence and prevalence of atrial fibrillation and associated mortality among Medicare beneficiaries, 1993-2007. *Circ Cardiovasc Qual Outcomes* 2012;5:85-93.
 31. Tsang TS, Gersh BJ, Appleton CP, et al. Left ventricular diastolic dysfunction as a predictor of the first diagnosed nonvalvular atrial fibrillation in 840 elderly men and women. *J Am Coll Cardiol* 2002;40:1636-44.
 32. Tsang TS, Barnes ME, Gersh BJ, et al. Risks for atrial fibrillation and congestive heart failure in patients ≥ 65 years of age with abnormal left ventricular diastolic

- relaxation. *Am J Cardiol* 2004;93:54-8.
33. Paulus WJ, Tschöpe C. A novel paradigm for heart failure with preserved ejection fraction: comorbidities drive myocardial dysfunction and remodeling through coronary microvascular endothelial inflammation. *J Am Coll Cardiol* 2013;62:263-71.
 34. Lam CSP, Lund LH. Microvascular endothelial dysfunction in heart failure with preserved ejection fraction. *Heart* 2016;102:257-9.
 35. Frustaci A, Chimenti C, Bellocci F, et al. Histological substrate of atrial biopsies in patients with lone atrial fibrillation. *Circulation* 1997;96:1180-4.
 36. Sasaki N, Okumura Y, Watanabe I, et al. Increased levels of inflammatory and extracellular matrix turnover biomarkers persist despite reverse atrial structural remodeling during the first year after atrial fibrillation ablation. *J Interv Card Electrophysiol* 2014;39:241-9.
 37. Melenovsky V, Borlaug BA, Rosen B, et al. Cardiovascular features of heart failure with preserved ejection fraction versus nonfailing hypertensive left ventricular hypertrophy in the urban Baltimore community: the role of atrial remodeling/dysfunction. *J Am Coll Cardiol* 2007;49:198-207.
 38. Knackstedt C, Gramley F, Schimpf T, et al. Association of echocardiographic atrial size and atrial fibrosis in a sequential model of congestive heart failure and atrial fibrillation. *Cardiovasc Pathol* 2008;17:318-24.
 39. Tanaka K, Zlochiver S, Vikstrom KL, et al. Spatial distribution of fibrosis governs fibrillation wave dynamics in the posterior left atrium during heart failure. *Circ Res* 2007;101:839-47.

40. Sanders P, Morton JB, Davidson NC, et al. Electrical remodeling of the atria in congestive heart failure: electrophysiological and electroanatomic mapping in humans. *Circulation* 2003;108:1461-8.
41. Li D, Melnyk P, Feng J, et al. Effects of experimental heart failure on atrial cellular and ionic electrophysiology. *Circulation* 2000;101:2631-8.
42. Cha TJ, Ehrlich JR, Zhang L, et al. Dissociation between ionic remodeling and ability to sustain atrial fibrillation during recovery from experimental congestive heart failure. *Circulation* 2004;109:412-8.
43. Yeh YH, Wakili R, Qi XY, et al. Calcium-handling abnormalities underlying atrial arrhythmogenesis and contractile dysfunction in dogs with congestive heart failure. *Circ Arrhythm Electrophysiol* 2008;1:93-102.
44. Hsieh MH, Lin YJ, Wang HH, et al. Functional characterization of atrial electrograms in a pacing-induced heart failure model of atrial fibrillation: importance of regional atrial connexin40 remodeling. *J Cardiovasc Electrophysiol* 2013;24:573-82.
45. Kitzman DW, Little WC, Brubaker PH, et al. Pathophysiological characterization of isolated diastolic heart failure in comparison to systolic heart failure. *JAMA* 2002;288:2144-50.
46. McKie PM, Schirger JA, Costello-Boerrigter LC, et al. Impaired natriuretic and renal endocrine response to acute volume expansion in pre-clinical systolic and diastolic dysfunction. *J Am Coll Cardiol* 2011;58:2095-103.
47. Casaclang-Verzosa G, Gersh BJ, Tsang TS. Structural and functional remodeling of the left atrium: clinical and therapeutic implications for atrial fibrillation. *J Am Coll Cardiol* 2008;51:1-11.

48. Manning WJ, Silverman DI, Katz SE, et al. Impaired left atrial mechanical function after cardioversion: relation to the duration of atrial fibrillation. *J Am Coll Cardiol* 1994;23:1535-40.
49. Shite J, Yokota Y, Yokoyama M. Heterogeneity and time course of improvement in cardiac function after cardioversion of chronic atrial fibrillation: assessment of serial echocardiographic indices. *Br Heart J* 1993;70:154-9.
50. Shantsila E, Shantsila A, Blann AD, et al. Left ventricular fibrosis in atrial fibrillation. *Am J Cardiol* 2013;111:996-1001.
51. Zile MR, Baicu CF, Ikonomidis JS, et al. Myocardial stiffness in patients with heart failure and a preserved ejection fraction: contributions of collagen and titin. *Circulation* 2015;131:1247-59.
52. Pai RG, Varadarajan P, Tanimoto M. Effect of atrial fibrillation on the dynamics of mitral annular area. *J Heart Valve Dis* 2003;12:31-7.
53. van den Berg MP, van Gelder IC, van Veldhuisen DJ. Depletion of atrial natriuretic peptide during longstanding atrial fibrillation. *Europace* 2004;6:433-7.
54. Ellis ER, Josephson ME. Heart failure and tachycardia-induced cardiomyopathy. *Curr Heart Fail Rep* 2013;10:296-306.
55. Daoud EG, Weiss R, Bahu M, et al. Effect of an irregular ventricular rhythm on cardiac output. *Am J Cardiol* 1996;78:1433-6.
56. Authors/Task Force Members, McMurray JJV, Adamopoulos S, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012. *Eur Heart J* 2012;33:1787-847.
57. Ferrari R, Böhm M, Cleland JG, et al. Heart failure with preserved ejection fraction:

- uncertainties and dilemmas. *Eur J Heart Fail* 2015;17:665-71.
58. Basaraba JE, Barry AR. Pharmacotherapy of heart failure with preserved ejection fraction. *Pharmacotherapy* 2015;35:351-60.
 59. Sohn DW, Song JM, Zo JH, et al. Mitral annulus velocity in the evaluation of left ventricular diastolic function in atrial fibrillation. *J Am Soc Echocardiogr* 1999;12:927-31.
 60. Sénéchal M, O'Connor K, Deblois J, et al. A simple Doppler echocardiography method to evaluate pulmonary capillary wedge pressure in patients with atrial fibrillation. *Echocardiography* 2008;25:57-63.
 61. Kusunose K, Yamada H, Nishio S, et al. Clinical utility of single-beat E/e' obtained by simultaneous recording of flow and tissue Doppler velocities in atrial fibrillation with preserved systolic function. *J Am Coll Cardiol Img* 2009;2:1147-56.
 62. Li C, Zhang J, Zhou C, Huang L, et al. Will simultaneous measurement of E/e' index facilitate the non-invasive assessment of left ventricular filling pressure in patients with non-valvular atrial fibrillation? *Eur J Echocardiogr* 2010;11:296-301.
 63. Wada Y, Murata K, Tanaka T, et al. Simultaneous Doppler tracing of transmitral inflow and mitral annular velocity as an estimate of elevated left ventricular filling pressure in patients with atrial fibrillation. *Circ J* 2012;76:675-81.
 64. Okura H, Takada Y, Kubo T, et al. Tissue Doppler-derived index of left ventricular filling pressure, E/E', predicts survival of patients with non-valvular atrial fibrillation. *Heart* 2006;92:1248-52.
 65. Lee SH, Jung JH, Choi SH, et al. Exercise intolerance in patients with atrial fibrillation: clinical and echocardiographic determinants of exercise capacity. *J Am*

- Soc Echocardiogr 2005;18:1349-54.
66. Lee SH, Choi S, Chung WJ, et al. Tissue Doppler index, E/E', and ischemic stroke in patients with atrial fibrillation and preserved left ventricular ejection fraction. J Neurol Sci 2008;271:148-52.
 67. Punjani S, Wu WC, Cohen S, et al. Echocardiographic indices of diastolic function relate to functional capacity and quality of life in ambulatory men with atrial fibrillation. J Am Soc Echocardiogr 2011;24:533-540.e3.
 68. Donal E, Lip GY, Galderisi M, et al. EACVI/EHRA Expert Consensus Document on the role of multi-modality imaging for the evaluation of patients with atrial fibrillation. Eur Heart J Cardiovasc Imaging 2016;17:355-83.
 69. Santos AB, Kraigher-Krainer E, Gupta DK, et al.; PARAMOUNT Investigators. Impaired left atrial function in heart failure with preserved ejection fraction. Eur J Heart Fail 2014;16:1096-103.
 70. Nagueh SF, Appleton CP, Gillebert TC, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. Eur J Echocardiogr 2009;10:165-93.
 71. Olsson LG, Swedberg K, Ducharme A, et al.; CHARM Investigators. Atrial fibrillation and risk of clinical events in chronic heart failure with and without left ventricular systolic dysfunction: results from the Candesartan in Heart failure- Assessment of Reduction in Mortality and morbidity (CHARM) program. J Am Coll Cardiol 2006;47:1997-2004.
 72. Santhanakrishnan R, Wang N, Larson MG, et al. Atrial fibrillation begets heart failure and vice versa: temporal associations and differences in preserved versus reduced

- ejection fraction. *Circulation* 2016;133:484-92.
73. Oluleye OW, Rector TS, Win S, et al. History of atrial fibrillation as a risk factor in patients with heart failure and preserved ejection fraction. *Circ Heart Fail* 2014;7:960-6.
 74. Lam CS, Carson PE, Anand IS, et al. Sex differences in clinical characteristics and outcomes in elderly patients with heart failure and preserved ejection fraction: the Irbesartan in Heart Failure with Preserved Ejection Fraction (I-PRESERVE) trial. *Circ Heart Fail* 2012;5:571-8.
 75. Fung JW, Sanderson JE, Yip GW, et al. Impact of atrial fibrillation in heart failure with normal ejection fraction: a clinical and echocardiographic study. *J Card Fail* 2007;13:649-55.
 76. January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the Heart Rhythm Society. *J Am Coll Cardiol* 2014;64:2246-80.
 77. Cleland JG, Tendera M, Adamus J. et al.; PEP-CHF Investigators. The Perindopril in Elderly People with Chronic Heart Failure (PEP-CHF) study. *Eur Heart J* 2006;27:2338-45.
 78. Massie BM, Carson PE, McMurray JJ, et al.; I-PRESERVE Investigators. Irbesartan in patients with heart failure and preserved ejection fraction. *N Engl J Med* 2008;359:2456-67.
 79. Yusuf S, Pfeffer MA, Swedberg K, et al.; CHARM Investigators and Committees. Effects of candesartan in patients with chronic heart failure and preserved left-

- ventricular ejection fraction: the CHARM-Preserved Trial. *Lancet* 2003;362:777-81.
80. Ziff OJ, Lane DA, Samra M, et al. Safety and efficacy of digoxin: systematic review and meta-analysis of observational and controlled trial data. *BMJ* 2015;351:h4451.
 81. Sandhu RK, Hohnloser SH, Pfeffer MA, et al. Relationship between degree of left ventricular dysfunction, symptom status, and risk of embolic events in patients with atrial fibrillation and heart failure. *Stroke* 2015;46:667-72.
 82. Kotecha D, Banerjee A, Lip GY. Increased stroke risk in atrial fibrillation patients with heart failure: does ejection fraction matter? *Stroke* 2015;46:608-9.
 83. Xiong Q, Lau YC, Senoo K, et al. Non-vitamin K antagonist oral anticoagulants (NOACs) in patients with concomitant atrial fibrillation and heart failure: a systemic review and meta-analysis of randomized trials. *Eur J Heart Fail* 2015;17:1192-200.
 84. Abed HS, Wittert GA, Leong DP, et al. Effect of weight reduction and cardiometabolic risk factor management on symptom burden and severity in patients with atrial fibrillation: a randomized clinical trial. *JAMA* 2013;310:2050-60.
 85. Pathak RK, Middeldorp ME, Meredith M, et al. Long-term effect of goal-directed weight management in an atrial fibrillation cohort: a long-term follow-up study (LEGACY). *J Am Coll Cardiol* 2015;65:2159-69.
 86. Pathak RK, Middeldorp ME, Lau DH, et al. Aggressive risk factor reduction study for atrial fibrillation and implications for the outcome of ablation: the ARREST-AF cohort study. *J Am Coll Cardiol* 2014;64:2222-31.
 87. Pathak RK, Elliott A, Middeldorp ME, et al. Impact of CARDIOrespiratory FITness on Arrhythmia Recurrence in obese individuals with atrial fibrillation: the CARDIO-FIT Study. *J Am Coll Cardiol* 2015;66:985-96.

88. Kitzman DW, Brubaker P, Morgan T, et al. Effect of caloric restriction or aerobic exercise training on peak oxygen consumption and quality of life in obese older patients with heart failure with preserved ejection fraction: a randomized clinical trial. JAMA 2016;315:36-46.
89. University of Birmingham. Rate Control Therapy Evaluation in Permanent Atrial Fibrillation (RATE-AF). In: ClinicalTrials.gov. Bethesda, MD: National Library of Medicine. 2016. Available at: <https://clinicaltrials.gov/ct2/show/NCT02391337>. Accessed August 29, 2016.
90. Groenveld HF, Crijns HJGM, Van den Berg MP, et al.; RACE II Investigators. The effect of rate control on quality of life in patients with permanent atrial fibrillation: data from the RACE II (Rate Control Efficacy in Permanent Atrial Fibrillation II) Study. J Am Coll Cardiol 2011;58:1795-803.
91. Grönefeld GC, Lilienthal J, Kuck KH, et al. Impact of rate versus rhythm control on quality of life in patients with persistent atrial fibrillation. Eur Heart J 2003;24:1430-6.
92. Machino-Ohtsuka T, Seo Y, Ishizu T, et al. Efficacy, safety, and outcomes of catheter ablation of atrial fibrillation in patients with heart failure with preserved ejection fraction. J Am Coll Cardiol 2013;62:1857-65.
93. Aliot E, Brandes A, Eckardt L, et al. The EAST study: redefining the role of rhythm control therapy in atrial fibrillation. Eur Heart J 2015;36:255-6.
94. Butler J, Fonarow GC, Zile MR, et al. Developing therapies for heart failure with preserved ejection fraction: current state and future directions. J Am Coll Cardiol HF 2014;2:97-112.

95. Solomon SD, Zile M, Pieske B, et al.; Prospective comparison of ARNI with ARB on Management Of heart failUre with preserved ejection fracTion (PARAMOUNT) Investigators. The angiotensin receptor neprilysin inhibitor LCZ696 in heart failure with preserved ejection fraction: a phase 2 double-blind randomised controlled trial. *Lancet* 2012;380:1387-95.
96. McMurray JJ, Packer M, Desai AS, et al.; PARADIGM-HF Investigators and Committees. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med* 2014;371:993-1004.
97. Chan MM, Lam CS. How do patients with heart failure with preserved ejection fraction die? *Eur J Heart Fail* 2013;15:604-13.
98. Adabag S, Rector TS, Anand IS, et al. A prediction model for sudden cardiac death in patients with heart failure and preserved ejection fraction. *Eur J Heart Fail* 2014;16:1175-82.
99. University Medical Center Groningen. Ventricular Tachyarrhythmia Detection by Implantable Loop Recording in Patients With Heart Failure and Preserved Ejection Fraction (VIP-HF). In: *ClinicalTrials.gov*. Bethesda, MD: National Library of Medicine. 2016. Available at: <https://clinicaltrials.gov/ct2/show/NCT01989299>. Accessed August 29, 2016
100. Hai OY, Mentz RJ, Zannad F, et al. Cardiac resynchronization therapy in heart failure patients with less severe left ventricular dysfunction. *Eur J Heart Fail* 2015;17:135-43.
101. Menet A, Greffe L, Ennezat PV, et al. Is mechanical dyssynchrony a therapeutic target in heart failure with preserved ejection fraction? *Am Heart J* 2014;168:909-

- 16.e1.
102. Rosenberg MA, Manning WJ. Diastolic dysfunction and risk of atrial fibrillation: a mechanistic appraisal. *Circulation* 2012;126:2353-62.
 103. Adamson PB, Abraham WT, Bourge RC, et al. Wireless pulmonary artery pressure monitoring guides management to reduce decompensation in heart failure with preserved ejection fraction. *Circ Heart Fail* 2014;7:935-44.

FIGURE LEGENDS

Central Illustration: Diagnosis and Management of Concomitant HFpEF and AF

*The ratio of mitral peak E velocity to tissue Doppler e': >15 septal and >13 lateral are associated with adverse outcomes in AF patients. Other indexes are also helpful, such as mitral deceleration time, isovolumic relaxation time and pulmonary venous flow. Note that echocardiographic determination of diastolic dysfunction is different in patients with AF due to the lack of mitral inflow A wave, loss of pulmonary venous flow A reversal and different "normal value: ranges compared to sinus rhythm (e.g., diminution of pulmonary venous systolic flow in AF). †NT-proBNP ≥ 600 pg/ml, as used in the SOCRATES-Preserved study (NCT01951638), or >900 pg/ml, used in the PARAGON-HF trial (NCT01920711). AF = atrial fibrillation; ECG = electrocardiogram; HFpEF = heart failure with preserved ejection fraction; NOAC = nonvitamin K antagonist oral anticoagulant; VKA = vitamin K antagonist oral anticoagulant.

Figure 1: Prevalence of HFpEF in AF

The prevalence of HFpEF in 4 major AF trials. The percentage with left ventricular ejection fraction above 40% or 50% is indicated in the columns, as is the type of AF. AF = atrial fibrillation; HFpEF = heart failure with preserved ejection fraction.

Figure 2: Prevalence of AF in HFpEF

The prevalence of AF in HFpEF varies in 7 large heart failure trials. Abbreviations as in **Figure 1**.

Figure 3: Pathophysiology and Shared Mechanisms in HFpEF and AF.

Common mechanisms involved in HFpEF, AF, and the combination of these conditions. ANP = atrial natriuretic peptide; LV = left ventricular; RAAS = renin-angiotensin-aldosterone system.

Other abbreviations as in **Figure 1**.

Table 1. Knowledge Gaps and Areas Essential for Advancing Understanding of the Pathogenesis, Prevention, and Treatment of Concomitant HFpEF and AF

Research Domain	Important Knowledge Gaps	Areas of Potential Discovery and Scientific Advancement
Epidemiology	<p>Incidence and prevalence of HFpEF in the setting of AF.</p> <p>Global burden of HFpEF and AF.</p>	<p>Identification of the clinical, subclinical, and genomic factors underlying variability in AF and HFpEF, life course, and complications in diverse racial groups, populations and regions.</p> <p>Discovery of strategies to prevent AF onset and progression in the setting of HFpEF, and vice versa.</p>
Noninvasive imaging	<p>Diagnosis of HFpEF in the setting of AF.</p>	<p>Novel methods for assessing diastolic function and, in particular, for quantifying LA function are within reach. Measuring LA volume using 3-dimensional echocardiography, quantifying LA function with speckle-based strain and velocity vector imaging (102).</p>
Natriuretic peptides	<p>Optimal cutoff values for diagnosis of HFpEF in</p>	<p>Clinical classification of patients to enable stratified therapy and a more</p>

	patients with AF.	personalized approach.
Clinical cardiology	<p>Treatment of AF in the setting of HFpEF.</p> <p>Treatment of HFpEF in the setting of AF.</p>	<p>Investigation of rate and rhythm control in AF and HFpEF, and improvement in symptom burden and prognosis.</p> <p>Confirmation that the benefits of physical activity and lifestyle modification seen in HFpEF (88) and AF (87) also occur in patients with both conditions.</p> <p>Development of novel therapeutic agents in patients with HFpEF that are also beneficial in those with concomitant AF.</p> <p>Further data on patient care managed by hemodynamic monitoring (103)</p> <p>Investigation of device therapies in AF and HFpEF.</p>
Systems biology	Relations between clinical risk factors, genetics, and environment.	<p>Integration across multiple disciplines (basic science, epidemiological, clinical, bioinformatics) will accelerate our understanding of complex pathways underlying AF and HFpEF, and develop opportunities for prevention and treatment.</p>

AF = atrial fibrillation; HFpEF = heart failure with preserved ejection fraction; LA = left atrium/atrial



Diagnosis of atrial fibrillation (AF) and heart failure with preserved ejection fraction (HFpEF)

	HFpEF	AF	Combined
Symptoms			
Breathlessness	+	+	++
Fatigue	+	+	++
Orthopnea	+	—	+
Nocturnal dyspnea	+	—	+
Signs			
Increased venous pressure	+	—	+
Rales/third heart sound	+	—	+
Irregular pulse	—	+	+
Investigations			
AF on ECG or device	—	+	+
Left atrial enlargement	+	+	++
Increased E/e _o ratio on echo*	+	—	+
Increased natriuretic peptides [†]	+	+	++
Clinical response to diuretics	+	—	+



Treatment recommendations for AF and HFpEF

Prognostic

Anticoagulation with NOACs or VKA
(all patients ≥65 years or other risk factors)

Disease modifying

- Anti-hypertensive therapy
- Treatment of myocardial ischemia
- Management of associated comorbidities

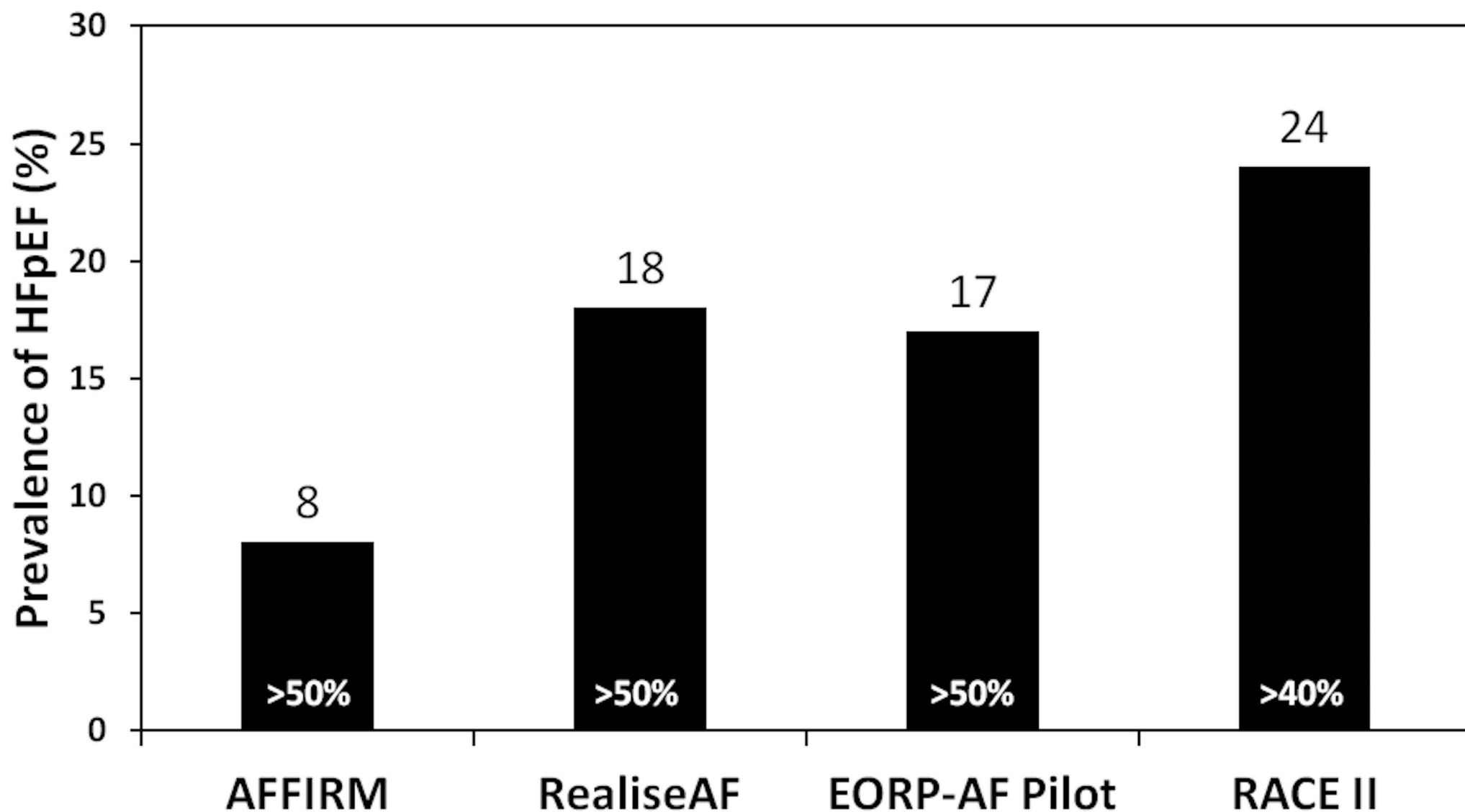
Symptomatic therapy

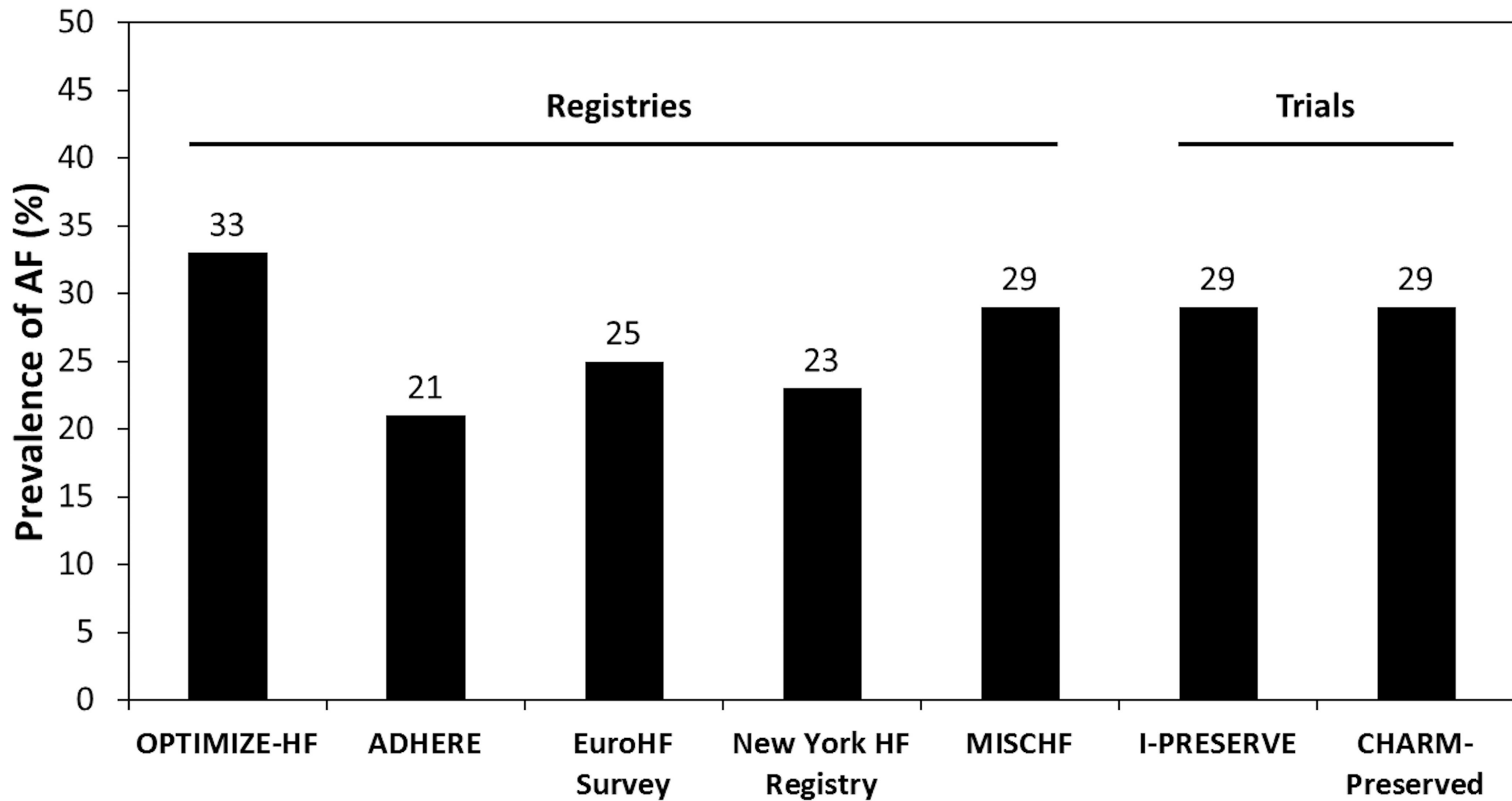
- Diuretics
- Heart rate control (resting <110 bpm;
lower if ongoing symptoms)
- AF rhythm control

Paroxysmal/
persistent AF

All types of AF

Persistent AF





HFpEF

LV hypertrophy and fibrosis
Diastolic dysfunction

Reduced ventricular filling
LV myocardial fibrosis
Diastolic dysfunction

Common risk factors:
· Hypertension
· Aging
· Obesity
· Obstructive sleep apnea syndrome

- Systemic inflammation
- Neurohormonal activation
- Up regulation of RAAS
- Endothelial dysfunction
- Reduced ANP release
- Annular remodeling (mitral valve and tricuspid valve regurgitation)
- Chronotropic incompetence and tachycardia induced cardiomyopathy

Left atrial enlargement and stretch

Atrial fibrosis

(Abnormal distribution of GAP junctions and loss of cell-to-cell coupling)

Electrical remodeling and increased atrial refractoriness

AF

Maintenance of AF



AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION
AUTHOR RESPONSIBILITIES: RELATIONSHIP WITH INDUSTRY AND FINANCIAL DISCLOSURE

In addition to disclosing relationship with industry and/or financial disclosures on the *cover letter* and *title* page of your manuscript, we ask that each author sign this form.

To be published in the following journal (please check):

☒ *Journal of the American College of Cardiology(JACC)* ☐ *JACC: Cardiovascular Interventions* ☐ *JACC: Cardiovascular Imaging* ☐ *JACC: Heart Failure* ☐ *JACC: Clinical Electrophysiology* ☐ *JACC: Basic Translational Science*

Article entitled: Vicious Twins - Heart Failure with Preserved Ejection Fraction and Atrial Fibrillation

Manuscript number: JACC080316-3226N

Corresponding Author: Dr. Rienstra

Corresponding author's printed name: Michiel Rienstra

***Corresponding Author's Responsibility**

To avoid delay in the publication of your manuscript, **complete and submit this form as quickly as possible.**

After you have submitted your electronic form, you will receive an email confirmation that includes a PDF copy. Please print and retain for your files. **If for some reason you are unable to complete this form electronically**, please contact the JACC office directly or print this form, fill in the spaces manually, and email, fax, or post mail a copy to:

Journal of the American College of Cardiology(JACC)

JACC: Cardiovascular Interventions

JACC: Cardiovascular Imaging

JACC: Heart Failure

JACC: Clinical Electrophysiology

JACC: Basic Translational Science

Heart House, 2400 N Street NW, Washington, DC, 20037

Fax: (202) 375-6819

Email: jaccsd@acc.org jaccint@acc.org jaccimg@acc.org jacchf@acc.org jacccep@acc.org jaccbtr@acc.org

Complete the section below, type your name into the Type Name box and input the date. *By submitting this form, you attest to being an author on the paper.*

Type Name: Dipak Kotecha Date: 25 AUG 2016

Title and Company (if employer representative): Clinician Scientist, University of Birmingham

I have **relationship with industry** to disclose.

1. Type **relationship with industry** to disclose: Research grant from Menarini
2. Type **relationship with industry** to disclose: Lecture fees from AtriCure
3. Type **relationship with industry** to disclose: Professional development support from Daiichi Sankyo

I have **no financial information** to disclose.

local_p_id: 296242

time: 1472161914

ip address: 10.10.1.19



AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION
AUTHOR RESPONSIBILITIES: RELATIONSHIP WITH INDUSTRY AND FINANCIAL DISCLOSURE

In addition to disclosing relationship with industry and/or financial disclosures on the *cover letter* and *title* page of your manuscript, we ask that each author sign this form.

To be published in the following journal (please check):

☒ *Journal of the American College of Cardiology(JACC)* ☐ *JACC: Cardiovascular Interventions* ☐ *JACC: Cardiovascular Imaging* ☐ *JACC: Heart Failure* ☐ *JACC: Clinical Electrophysiology* ☐ *JACC: Basic Translational Science*

Article entitled: Vicious Twins - Heart Failure with Preserved Ejection Fraction and Atrial Fibrillation

Manuscript number: JACC080316-3226N

Corresponding Author: Dr. Rienstra

Corresponding author's printed name: Michiel Rienstra

***Corresponding Author's Responsibility**

To avoid delay in the publication of your manuscript, **complete and submit this form as quickly as possible.**

After you have submitted your electronic form, you will receive an email confirmation that includes a PDF copy. Please print and retain for your files. **If for some reason you are unable to complete this form electronically**, please contact the JACC office directly or print this form, fill in the spaces manually, and email, fax, or post mail a copy to:

Journal of the American College of Cardiology(JACC)

JACC: Cardiovascular Interventions

JACC: Cardiovascular Imaging

JACC: Heart Failure

JACC: Clinical Electrophysiology

JACC: Basic Translational Science

Heart House, 2400 N Street NW, Washington, DC, 20037

Fax: (202) 375-6819

Email: jaccsd@acc.org jaccint@acc.org jaccimg@acc.org jacchf@acc.org jacccep@acc.org jaccbtr@acc.org

Complete the section below, type your name into the Type Name box and input the date. *By submitting this form, you attest to being an author on the paper.*

Type Name: Carolyn Lam Date: 25 Aug 2016

Title and Company (if employer representative):

I have **relationship with industry** to disclose.

1. Type **relationship with industry** to disclose: I have received research support from Boston Scientific, Bayer, Thermofisher, Medtronic, and Vifor Pharma; and have consulted for Bayer, Novartis, Takeda, Merck, Astra Zeneca, Janssen Research & Development, LLC, Menarini, Boehringer Ingelheim and Abbott Diagnostics

I have **no financial information** to disclose.

local_p_id: 172966

time: 1472056538

ip address: 10.10.1.19



AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION
AUTHOR RESPONSIBILITIES: RELATIONSHIP WITH INDUSTRY AND FINANCIAL DISCLOSURE

In addition to disclosing relationship with industry and/or financial disclosures on the *cover letter* and *title* page of your manuscript, we ask that each author sign this form.

To be published in the following journal (please check):

☒ *Journal of the American College of Cardiology(JACC)* ☐ *JACC: Cardiovascular Interventions* ☐ *JACC: Cardiovascular Imaging* ☐ *JACC: Heart Failure* ☐ *JACC: Clinical Electrophysiology* ☐ *JACC: Basic Translational Science*

Article entitled: Vicious Twins - Heart Failure with Preserved Ejection Fraction and Atrial Fibrillation

Manuscript number: JACC080316-3226N

Corresponding Author: Dr. Rienstra

Corresponding author's printed name: Rienstra

***Corresponding Author's Responsibility**

To avoid delay in the publication of your manuscript, **complete and submit this form as quickly as possible.**

After you have submitted your electronic form, you will receive an email confirmation that includes a PDF copy. Please print and retain for your files. **If for some reason you are unable to complete this form electronically**, please contact the JACC office directly or print this form, fill in the spaces manually, and email, fax, or post mail a copy to:

Journal of the American College of Cardiology(JACC)

JACC: Cardiovascular Interventions

JACC: Cardiovascular Imaging

JACC: Heart Failure

JACC: Clinical Electrophysiology

JACC: Basic Translational Science

Heart House, 2400 N Street NW, Washington, DC, 20037

Fax: (202) 375-6819

Email: jaccsd@acc.org jaccint@acc.org jaccimg@acc.org jacchf@acc.org jacccep@acc.org jaccbtr@acc.org

Complete the section below, type your name into the Type Name box and input the date. *By submitting this form, you attest to being an author on the paper.*

Type Name: Dirk van Veldhuisen Date: August 24, 2016

Title and Company (if employer representative): --

I have **no relationship with industry** to disclose.

I have **no financial information** to disclose.

local_p_id: 117227

time: 1472051641

ip address: 10.10.1.19



AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION
AUTHOR RESPONSIBILITIES: RELATIONSHIP WITH INDUSTRY AND FINANCIAL DISCLOSURE

In addition to disclosing relationship with industry and/or financial disclosures on the *cover letter* and *title* page of your manuscript, we ask that each author sign this form.

To be published in the following journal (please check):

☒ *Journal of the American College of Cardiology(JACC)* ☐ *JACC: Cardiovascular Interventions* ☐ *JACC: Cardiovascular Imaging* ☐ *JACC: Heart Failure* ☐ *JACC: Clinical Electrophysiology* ☐ *JACC: Basic Translational Science*

Article entitled: Vicious Twins - Heart Failure with Preserved Ejection Fraction and Atrial Fibrillation

Manuscript number: JACC080316-3226N

Corresponding Author: Dr. Rienstra

Corresponding author's printed name: Isabelle C Van Gelder

***Corresponding Author's Responsibility**

To avoid delay in the publication of your manuscript, **complete and submit this form as quickly as possible.**

After you have submitted your electronic form, you will receive an email confirmation that includes a PDF copy. Please print and retain for your files. **If for some reason you are unable to complete this form electronically**, please contact the JACC office directly or print this form, fill in the spaces manually, and email, fax, or post mail a copy to:

Journal of the American College of Cardiology(JACC)

JACC: Cardiovascular Interventions

JACC: Cardiovascular Imaging

JACC: Heart Failure

JACC: Clinical Electrophysiology

JACC: Basic Translational Science

Heart House, 2400 N Street NW, Washington, DC, 20037

Fax: (202) 375-6819

Email: jaccsd@acc.org jaccint@acc.org jaccimg@acc.org jacchf@acc.org jacccep@acc.org jaccbtr@acc.org

Complete the section below, type your name into the Type Name box and input the date. *By submitting this form, you attest to being an author on the paper.*

Type Name: Isabelle C Van Gelder Date: August 25 2016

Title and Company (if employer representative):

I have **no relationship with industry** to disclose.

I have **no financial information** to disclose.

local_p_id: 414613

time: 1472102731

ip address: 10.10.1.19



AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION
AUTHOR RESPONSIBILITIES: RELATIONSHIP WITH INDUSTRY AND FINANCIAL DISCLOSURE

In addition to disclosing relationship with industry and/or financial disclosures on the *cover letter* and *title* page of your manuscript, we ask that each author sign this form.

To be published in the following journal (please check):

☒ *Journal of the American College of Cardiology(JACC)* ☐ *JACC: Cardiovascular Interventions* ☐ *JACC: Cardiovascular Imaging* ☐ *JACC: Heart Failure* ☐ *JACC: Clinical Electrophysiology* ☐ *JACC: Basic Translational Science*

Article entitled: Vicious Twins - Heart Failure with Preserved Ejection Fraction and Atrial Fibrillation

Manuscript number: JACC080316-3226N

Corresponding Author: Dr. Rienstra

Corresponding author's printed name: Michiel Rienstra

***Corresponding Author's Responsibility**

To avoid delay in the publication of your manuscript, **complete and submit this form as quickly as possible.**

After you have submitted your electronic form, you will receive an email confirmation that includes a PDF copy. Please print and retain for your files. **If for some reason you are unable to complete this form electronically**, please contact the JACC office directly or print this form, fill in the spaces manually, and email, fax, or post mail a copy to:

Journal of the American College of Cardiology(JACC)

JACC: Cardiovascular Interventions

JACC: Cardiovascular Imaging

JACC: Heart Failure

JACC: Clinical Electrophysiology

JACC: Basic Translational Science

Heart House, 2400 N Street NW, Washington, DC, 20037

Fax: (202) 375-6819

Email: jaccsd@acc.org jaccint@acc.org jaccimg@acc.org jacchf@acc.org jacccep@acc.org jaccbtr@acc.org

Complete the section below, type your name into the Type Name box and input the date. *By submitting this form, you attest to being an author on the paper.*

Type Name: Adriaan Voors Date: August 24, 2016

Title and Company (if employer representative): UMCG

I have **no relationship with industry** to disclose.

I have **no financial information** to disclose.

local_p_id: 149489

time: 1472051068

ip address: 10.10.1.19



AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION
AUTHOR RESPONSIBILITIES: RELATIONSHIP WITH INDUSTRY AND FINANCIAL DISCLOSURE

In addition to disclosing relationship with industry and/or financial disclosures on the *cover letter* and *title* page of your manuscript, we ask that each author sign this form.

To be published in the following journal (please check):

☒ *Journal of the American College of Cardiology(JACC)* ☐ *JACC: Cardiovascular Interventions* ☐ *JACC: Cardiovascular Imaging* ☐ *JACC: Heart Failure* ☐ *JACC: Clinical Electrophysiology* ☐ *JACC: Basic Translational Science*

Article entitled: Vicious Twins - Heart Failure with Preserved Ejection Fraction and Atrial Fibrillation

Manuscript number: JACC080316-3226N

Corresponding Author: Dr. Rienstra

Corresponding author's printed name: michiel rienstra

***Corresponding Author's Responsibility**

To avoid delay in the publication of your manuscript, **complete and submit this form as quickly as possible.**

After you have submitted your electronic form, you will receive an email confirmation that includes a PDF copy. Please print and retain for your files. **If for some reason you are unable to complete this form electronically**, please contact the JACC office directly or print this form, fill in the spaces manually, and email, fax, or post mail a copy to:

Journal of the American College of Cardiology(JACC)

JACC: Cardiovascular Interventions

JACC: Cardiovascular Imaging

JACC: Heart Failure

JACC: Clinical Electrophysiology

JACC: Basic Translational Science

Heart House, 2400 N Street NW, Washington, DC, 20037

Fax: (202) 375-6819

Email: jaccsd@acc.org jaccint@acc.org jaccimg@acc.org jacchf@acc.org jacccep@acc.org jaccbtr@acc.org

Complete the section below, type your name into the Type Name box and input the date. *By submitting this form, you attest to being an author on the paper.*

Type Name: M. Rienstra Date: 28 aug 2016

Title and Company (if employer representative):

I have **no relationship with industry** to disclose.

I have **no financial information** to disclose.

local_p_id: 334143

time: 1472397516

ip address: 10.10.1.19